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| 09/890,604 | 03/01/2002 | David Dunham Ellis | 205502-9004 | 4587 |

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Michael Best & Friedrich
401 N Michigan Avenue Suite 1700
Chicago, IL 60611

| EXAMINER | |
|---|---|
| BAUM, STUART F | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1638 | |

DATE MAILED: 11/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/890,604 | ELLIS ET AL. | |
| | Examiner | Art Unit | |
| | Stuart F. Baum | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *10,12 and 28-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,13-27 and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/1/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-36 are pending.

2. Applicant's election without traverse of Group I, claims 1-9, 11, 13-27 and 31-36 in the reply filed on 8/24/2004 is acknowledged.

Claims 10, 12, and 28-30 are withdrawn from consideration for being drawn to non-elected inventions.

3. Claims 1-9, 11, 13-27 and 31-36 are examined in the present office action.

### *Oath/Declaration*

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the citizenship of each inventor.

### *Priority*

5. If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application, i.e., in the first line of the specification.

***Specification***

6. Objection is made to the Drawings/Brief Description of the Drawings for not incorporating SEQ ID NO's when referring to nucleic acid or amino acid sequences. 37 CFR 1.821(d) requires the use of the assigned sequence identifier (e.g. SEQ I.D. NO: X) in all instances where the description or claims of a patent application discuss sequences.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 6-7, and 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-7, and 19-20 recite the limitation "said substantially homologous gene" in claims 5 and 18. There is insufficient antecedent basis for this limitation in the claim.

***Written Description***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-9, 11, 13-27 and 31-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a process or transformed gymnosperms comprising an expressible transgene: 1) that results in modification of lignin composition in gymnosperm plants, 2) that encodes at least one enzyme affecting the phenylpropanoid pathway leading to the synthesis of lignin, 3) that encodes at least one enzyme enabling the production of sinapyl alcohol or other residues with a side group at the C-5 position of a monolignol ring, 4) that encodes at least one enzyme enabling the production of lignin containing syringyl residues or other residues with a side group at the C-5 position of a monolignol rings, 5) encoding ferulate 5-hydroxylase (F5H) or substantially equivalent function, 6) encoding an enzyme having at least 50% or 75% homology with said ferulate 5-hydroxylase.

Applicants disclose the nucleotide sequence of the F5H gene from Arabidopsis and the amino acid sequence of the F5H enzyme in Figure 4 (page 12, lines 24-27).

The Applicants do not identify essential regions of the F5H protein, nor do Applicants describe any polynucleotide sequences that exhibit 50% or 75% homology with said F5H, or enzymes that exhibit substantially equivalent function to said F5H, nor do Applicants disclose any other enzymes that modify lignin composition in gymnosperms, affect the phenylpropanoid pathway, enable the production of sinapyl alcohol, syringyl residues or other residues with a side group at the C-5 position of a monolignol ring.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. The court goes on to say, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of polynucleotide sequences encoding a F5H protein falling within the scope of the claimed genus of polynucleotides that encode enzymes that have substantially equivalent function to a F5H, or that exhibit 50% or 75% homology with F5H, or any polynucleotide that encodes any other enzyme that affects the phenylpropanoid pathway, or sinapyl alcohol, syringyl residues or other residues with a side group at the C-5 position of a monolignol ring that are involved in lignin biosynthesis. Applicants only describe a single nucleic acid sequence encoding F5H from Arabidopsis. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of polynucleotides. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential

for the F5H protein, it remains unclear what features identify an Arabidopsis F5H protein. Since the genus of F5H proteins or any proteins that affect the phenylpropanoid pathway, or proteins that affect sinapyl alcohol, syringyl residues or other residues with a C-5 position of a monolignol ring that are involved in lignin biosynthesis has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

***Enablement***

9. Claims 1-9, 11, 13-27 and 31-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are drawn to a process of producing a transformed gymnosperm plant transformed with at least one transgene that results in modification of lignin composition

compared to a non-transformed plant, comprising introducing into the plant a vector comprising a transgene that results in the modification of the lignin composition, regenerating transformed gymnosperm callus or shoots from the transformed cells, maturing embryos from the transformed callus or shoots and generating transformed plant embryos, seeds seedlings or plants from the matured embryos or shoots, wherein the vector comprises a transgene that encodes an enzyme affecting the phenylpropanoid pathway leading to the synthesis of lignin, wherein the enzyme is a ferulate 5-hydroxylase or an enzyme with substantially equivalent function, wherein the gymnosperm plant is from the order coniferales, wherein the species is *Picea*, *Pinus*, wherein the ferulate 5-hydroxylase is operably linked to a regulatory sequence, a transformed gymnosperm plant having a genome containing at least one expressible transgene that results in modification of lignin composition in the gymnosperm plant compared to a non-transformed plant, wherein the transgene encodes a ferulate 5-hydroxylase or an enzyme with substantially equivalent function, wherein said gymnosperm plant is from the order coniferales, wherein the species is *Picea glauca, Picea sitchesis*, *Picea engelmanii*, *Pinus taeda* or *Pinus radiata*, wherein said ferulate 5-hydroxylase transgene is operably linked to at least one regulatory sequence, wherein said regulatory sequence is a 35S promoter, a process of producing a transformed gymnosperm plant comprising the introduction of a transgene wherein the transgene produces a hydroxy group at the C-5 position of a monolignol ring, comprising introducing into the plant a vector comprising a transgene that produces a hydroxy group at the C-5 position of a monolignol ring, regenerating transformed gymnosperm callus or shoots from the transformed cells, maturing embryos from the transformed callus or shoots and generating transformed plant embryos, seeds seedlings or plants from the matured embryos or shoots, wherein the transgene

enables the hydroxylation at the C-5 position of a monolignol ring of a residue involved in the lignin biosynthetic pathway, and plants produced by said process.

Applicants disclose the F5H gene from Arabidopsis operably linked to the 35S promoter transformed into spruce (page 14, last paragraph). Applicants disclose that the F5H gene is disclosed in Figure 4 (page 12, lines 24-26) which corresponds to SEQ ID NO:1 encoding SEQ ID NO:2. Applicants disclose that over 500 transformed seedling from over 50 transformed lines have been grown in a greenhouse and exhibit no abnormal phenotypes or altered growth patterns (page 15, last paragraph). Applicants disclose that the introduced transgene is present in 14 different lines (page 17, first paragraph).

Applicants are not enabled for their invention. Applicants disclose that the transgene is present in the regenerated spruce, but Applicants have not disclosed that introduction of the Arabidopsis F5H gene operably linked to the 35S promoter affects the phenylpropanoid pathway, sinapyl alcohol, syringyl residues or other residues with a side group at the C-5 position of a monolignol ring, or modifies lignin composition, in any way.

Altering lignin content or lignin structure by transforming plants with genes known to be involved in lignin biosynthesis produces unpredictable results including plants whose development and morphology have been altered. Kajita et al (1997, Plant Science 128:109-118) teach overexpressing 4-coumarate:CoA ligase (4CL) in tobacco reduced the expression of endogenous 4CL proteins in the xylem and phloem tissues of tobacco, but they note that the reduced expression was not uniform throughout the tissues and in regions of the xylem exhibiting reduced 4CL protein, collapsed xylem vessels were observed (abstract). Franke et al (2000, Plant Journal 22(3):223-234) teach that the correct spatial and temporal expression of a

chimeric gene used to alter the activity of an endogenous gene whose activity is involved in lignin biosynthesis is crucial for a successful result. Franke et al teach ferulate 5-hydroxylase (F5H) which is a gene involved in lignin biosynthesis, operably linked to the C4H promoter significantly changed the lignin composition of transformed *Arabidopsis* plants compared to plants that had been transformed with the F5H gene operably linked to the constitutive 35S CaMV promoter (abstract). Even though the 35S CaMV promoter is constitutive, its temporal expression profile is not adequate to achieve the desired result.

The state-of-the-art is such that one of skill in the art cannot predict which nucleic acids that are 50% homologous to the Arabidopsis ferulate 5-hydroxylase will encode a protein with the same activity as said ferulate 5-hydroxylase. The prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex, and the positions within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of maintaining function are limited (Bowie et al, Science 247:1306-1310, 1990, see especially page 1306). Proteins may be sensitive to alterations in even a single amino acid in a sequence. For example, the replacement of a glycine residue located within the START domain of either the PHABULOSA or PHAVOLUTA protein receptor with either an alanine or aspartic acid residue, alters the sterol/lipid binding domain (McConnell et al, Nature 411 (6838):709-713, 2001, see especially page 710, left column, 2nd paragraph).

In the absence of guidance, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified sequences, either by using non-disclosed regions of the nucleic acid encoding the Arabidopsis F5H protein

as probes or by designing primers to undisclosed regions of the Arabidopsis F5H protein, and isolating or amplifying fragments, subcloning the fragments, or by subcloning any nucleic acid sequence from any organism, producing expression vectors and transforming plants therewith, in order to identify those, if any, that when over-expressed, modify lignin composition in a gymnosperm.

Therefore, given the breadth of the claims; the lack of guidance and examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to practice the claimed invention, and therefore the invention is not enabled.

***Claim Rejections - 35 USC § 102***

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 15-17, 21, and 24-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Bloksberg et al (September, 1996, U.S. Patent Number 5,850,020).

The claims are drawn to a transformed gymnosperm plant having a genome containing at least one expressible transgene that results in modification of lignin composition compared to a

untransformed wild type plant, wherein the expressible transgene encodes one enzyme that produces a side group at the C-5 position of a monolignol ring, wherein said gymnosperm plant is from the order coniferales, wherein the plant is *Pinus radiata*.

Bloksberg et al teach a pine plant comprising a nucleotide sequence (SEQ ID NO:6; see column 4, line 40) encoding an O-methyl transferase (OMT), which modulates lignin content (columns 24-26, claims 15-39). Bloksberg et al also teach that the pine plant is *Pinus radiata* (column 3, lines 16-20). By definition, a methyl transferase enzyme transfers a methyl group onto monolignol rings, wherein a methyl group would be transferred to the C-5 position of a monolignol ring. The Office interprets modulating lignin content to mean that lignin composition has been modified, and as such, Bloksberg et al anticipates the claimed invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-9, 11, 13-27, and 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapple (July 1997, WO 97/23599), in view of Walter et al (January, 1997, WO 97/01641).

The claims are drawn to a process of producing a transformed gymnosperm plant transformed with at least one transgene that results in modification of lignin composition

compared to a non-transformed plant, comprising introducing into the plant a vector comprising a transgene that results in the modification of the lignin composition, regenerating transformed gymnosperm callus or shoots from the transformed cells, maturing embryos from the transformed callus or shoots and generating transformed plant embryos, seeds seedlings or plants from the matured embryos or shoots, wherein the vector comprises a transgene that encodes an enzyme affecting the phenylpropanoid pathway leading to the synthesis of lignin, wherein the enzyme is a ferulate 5-hydroxylase or an enzyme with substantially equivalent function, wherein the gymnosperm plant is from the order coniferales, wherein the species is *Picea*, *Pinus*, wherein the ferulate 5-hydroxylase is operably linked to a regulatory sequence, a transformed gymnosperm plant having a genome containing at least one expressible transgene that results in modification of lignin composition in the gymnosperm plant compared to a non-transformed plant, wherein the transgene encodes a ferulate 5-hydroxylase or an enzyme with substantially equivalent function, wherein said gymnosperm plant is from the order coniferales, wherein the species is *Picea glauca, Picea sitchesis*, *Picea engelmanii*, *Pinus taeda* or *Pinus radiata*, wherein said ferulate 5-hydroxylase transgene is operably linked to at least one regulatory sequence, wherein said regulatory sequence is a 35S promoter, a process of producing a transformed gymnosperm plant comprising the introduction of a transgene wherein the transgene produces a hydroxy group at the C-5 position of a monolignol ring, comprising introducing into the plant a vector comprising a transgene that produces a hydroxy group at the C-5 position of a monolignol ring, regenerating transformed gymnosperm callus or shoots from the transformed cells, maturing embryos from the transformed callus or shoots and generating transformed plant embryos, seeds seedlings or plants from the matured embryos or shoots, wherein the transgene

enables the hydroxylation at the C-5 position of a monolignol ring of a residue involved in the lignin biosynthetic pathway, and plants produced by said process.

Chapple teaches Arabidopsis and tobacco plants transformed with a nucleic acid molecule that encodes the Arabidopsis ferulate-5-hydroxylase (F5H) enzyme operably linked to the 35S promoter. The transformed plants exhibited modulated levels of syringyl values compared to wild-type plants, which indicates that the lignin composition was modified (pages 20-24, Examples 1-5). Ferulate-5-hydroxylase catalyzes the conversion of ferulate to 5-hydroxyferulate (a hydroxylation reaction) and permits the production of sinapic acid and its subsequent metabolites including sinapoylmalate and syringly lignin(page 8, lines 27-30) which includes sinapyl alcohol or other residues with a side group at the C-5 position of a monolignol ring.

Chapple does not teach transformation of gymnosperm plants comprising introducing a vector into cells of a gymnosperm to produce transformed cells, regenerating transformed gymnosperm callus or shoots from said cells, maturing embryos from the transformed callus or shoots and generating transformed plant embryos, seeds, seedlings or plants from matured embryos or shoots, wherein the gymnosperm plant is from the order coniferales, wherein said plant is from the species *Picea*, *Pinus*, including *Picea glauca*, *Picea sitchesis*, or *Picea engelmanii*, *Pinus taeda* or *Pinus radiata*, or transformed gymnosperm plant expressing a transgene that encodes at least one enzyme enabling the production of a residue of lignin biosynthetic pathway with a side group at the C-5 position of a monolignol ring, during the biosynthesis of lignin.

Walter et al teach introduction of vector into gymnosperm tissue (page 11, line 1), and Walter et al teach selection of transformed *Pinus radiata* tissue on medium which maintained the tissue in an undifferentiated state and then allowing the tissue to undergo development to form embryos, which were subsequently allowed to germinate to form whole plants grown in a greenhouse (page 10, lines 6-19). Walter et al disclose that the method also works for *Pinus taeda* (page 5, lines 18-19 and pages 17-23). The Office interprets tissue maintained in an undifferentiated state to mean callus. Although Walter et al does not explicitly teach *Picea glauca*, *Picea sitchesis*, or *Picea engelmanii*, it would have been obvious to one of ordinary skill in the art to apply these method to said plants to produce transformed plants, given the absence of evidence to the contrary.

Given the recognition of those of ordinary skill in the art the value of producing transformed gymnosperms with altered lignin composition for production of timber and pulp and paper, in particular, the creation of plants with increased levels of syringyl residues in their lignin to facilitate its chemical degradation as taught by Chapple and Walter et al (page 1, lines 20-21; page 2, lines 28-30, respectively), it would have been obvious to one of ordinary skill in the art to utilize the method of modulating lignin composition by transforming a plant with a nucleic acid encoding the ferulate-5-hydroxylase enzyme as taught by Chapple and to combine that method with the teachings of Walter et al which disclose a method of introducing a transgene into gymnosperms, and the subsequent regeneration of transformed gymnosperms, so as to produce transformed gymnosperm plants comprising a genome containing a transgene that encodes an enzyme enabling the production of a residue of a lignin biosynthetic pathway with a side group at the C-5 position of a monolignol ring, during the biosysnthesis of lignin.

Thus the claimed invention would have been *prima facie* obvious as a whole to one of ordinary skill in the art at the time it was made, especially in the absence of evidence to the contrary.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart F. Baum whose telephone number is 571-272-0792. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Stuart F. Baum Ph.D.
Patent Examiner
Art Unit 1638
November 8, 2004

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600